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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/762,587	09/06/2001	Antonio Grillo-Lopez	PM0277847	5272

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/762,587	GRILLO-LOPEZ, ANTONIO	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 7 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 7 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/04/06 has been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claim 7 is being examined.

Claim Rejections - 35 USC § 103

Claim 7 remains rejected under 35 USC 103, as being obvious over Maloney et al, in view of Press et al, Kaminsky et al, 1996, and Kaminsky et al (US 6,287,537, filed 05/29/1998), and further in view of Wahl et al, for reasons already of record in paper of 04/04/05.

A. Applicant asserts that Applicant does not agree that patients who are reported not responding to non-radiolabeled rituximab treatment must be refractory. Applicant argues that "non-responsive" and "refractory" have distinct meaning for therapeutic oncologists. Applicant argues that "refractory" requires more than simply the absence of a response. Applicant asserts that, for example, a patient might not respond or might not respond fully to a standard dose of a particular therapeutic agent, but would respond to a higher dose of the same agent; such patient would be described as a nonresponder to the standard dose, but would not qualify as refractory.

Applicant argues that a refractory patient is one who is not expected to respond to the therapy at all.

Applicant asserts that typically, patients are described as refractory after they first exhibit an effective response to a drug, and later do not show a comparable response to the same drug. Such patients would be both relapsed and refractory. Applicant asserts that in the case with therapeutic anit-CD20 antibodies, it is reasonable to expect that patients having tumors that are not CD20-positive would be refractory to those antibodies, at least so long as the tumor cells continue not to express CD20.

Applicant asserts that some of the patients reported in Maloney trial were genuinely refractory to rituximab therapy, but the information provided in the reference does not reasonably allow one to reach that conclusion. Applicant asserts that all one can say that certain patients did not respond to the trial protocol.

Applicant's arguments in paper of 05/04/06 have been considered but are found not to be persuasive.

It is noted that the limitation that 1) a refractory patient is one who is not expected to respond to the therapy "at all", or 2) that the subject has to first exhibit an effective response to a drug, and later does not show a comparable response to the same drug, i.e. both relapsed and refractory is not recited in the claims.

Further, since the definition of "refractory" in the specification is not limiting, and since "refractory" encompasses "not responsive to treatment" (Webster's II Dictionary, 1994, page 988), the subject refractory to treatment with non-radiolabeled rituximab in the claimed method is reasonably interpreted as encompassing any subject having CD20-positive cell lymphoma,

wherein the subject is resistant or not responsive to said treatment, as manifested by not showing anti-tumor response. Which refractory subject is clearly the same as the 77% of NHL patients in the reference by Maloney et al, who express CD20 antigen, but who do not respond to the treatment with the non-radiolabeled anti-CD20 antibody.

Further, concerning subjects that do **not** express CD20, and thus resistant to treatment with non-radiolabeled rituximab, which is an anti-CD20 antibody, the claims do not encompass those subjects, and thus are not germane here. It is noted that Maloney et al teach that **only adults with relapsed NHL B-cell lymphoma, that express the CD20 antigen, were eligible for treatment** with the anti-CD20 antibody IDEC-C2B8 (Maloney et al, p.3266, second column, second paragraph, p.3267, first column, item under "Patients"). However, the overall response rate is only 33% (Maloney et al, p.3270, last line, bridging p.3271). In other words, NHL cells from 77% of those treated patients, that express the CD20 antigen, do not respond to the treatment with the non-radiolabeled anti-CD20 antibody.

B. Applicant further argues that to fully combine the teaching of Maloney et al and the secondary reference, it would be necessary to administer a saturating dose of unlabeled anti-B1 antibody to patients before administering the radiolabeled antibody, because Kaminsky et al (US 6,287537 B1) teach that the "saturation" is responsible for the observation that certain subjects only respond to a follow-up dose of 131-I labeled anti-B1, and indeed , is necessary to provide the full therapeutic effect of the radiolabeled anti-CD20 therapy. Applicant argues that it would not have been obvious to administer a saturating dose of an unlabeled anti-CD20 to any patient already known to be refractory to therapy with an unlabeled anti-CD20 antibody.

Applicant argues that the reference thus provides no motivation to combine their teaching that would lead to the practice the claimed invention.

Applicant's arguments in paper of 05/04/06 have been considered but are found not to be persuasive.

Contrary to Applicant's arguments, there is no indication from the Kaminsky reference (US 6,287,537, filed 05/29/1998) that one has to administer a "saturing" dose of non-radiolabeled anti-CD20 antibody to patients who **already refractory** to the treatment with non-radiolabeled anti-CD20 antibody, before administering the radiolabeled anti-CD20 antibody, to successfully treat those patients. It is noted that Kaminsky et al (US 6,287,537, filed 05/29/1998) teach treating NHL lymphoma patients, by administering non-radiolabeled anti-CD20 antibody followed by I-131 labeled anti-CD20 antibody (Examples 1-2 on columns 13-22). Kaminsky et al (US 6,287,537, filed 05/29/1998) teach that the anti-tumor response of the non-radiolabeled antibody alone is only seen after a large dose of the non-radiolabeled antibody (column 21, lines 40-54). This teaching clearly suggests that although the non-radiolabeled anti-CD20 antibody has some anti-tumor effect, it is not efficient, because a large amount of it is required to show its effect. Further, Kaminsky et al (US 6,287,537, filed 05/29/1998) teach that the radiolabeled anti-CD20 is effective in those cases wherein the patients do not respond to non-radiolabeled anti-CD20 alone (column 21, third paragraph, lines 48-54). Thus the teaching of Kaminsky et al (US 6,287,537, filed 05/29/1998) would motivate one to use the radiolabeled anti-CD20 antibody, as taught by Kaminsky et al (US 6,287,537, filed 05/29/1998), Press et al, Kaminsky et al, 1996, and Wahl et al, for treating patients that are resistant to or non-responsive to non-radiolabeled anti-CD20 antibody treatment, such as the 77% population of patients taught by Maloney et al,

because the radiolabeled anti-CD20 is effective in those patients that do not respond to non-radiolabeled anti-CD20 alone, as taught by Kaminsky et al, (US 6,287,537, filed 05/29/1998) and because the radiolabeled anti-CD20 is superior to the non-radiolabeled anti-CD20 alone, having a synergy of the anti-tumor effect by the antibody moiety, and the anti-tumor effect by radiation, as taught by Kaminsky et al (US 6,287,537, filed 05/29/1998), and because the non-radiolabeled anti-CD20 antibody has been shown not to be effective against these refractory population of B-lymphoma patients that express CD20, in view of the teaching of Maloney et al.

One would have a reasonable expectation of success, because the radiolabeled anti-CD20 is effective in those cases wherein the patients do not respond to non-radiolabeled anti-CD20 alone, as taught by Kaminsky et al, and because readministration of I-131 labeled anti-B1 antibody (murine anti-CD20) in patients with non-Hodgkin's lymphoma that are relapsed is safe, and effective, as taught by Wahl et al; and thus one would have expected that similarly it would be safe to administer I-131 labeled anti-B1 antibody (murine anti-CD20) in patients with B-cell lymphoma that have been previously treated with a non-labeled humanized anti-CD20 antibody, rituximab.

New Rejections Based On New Consideration

Claim Rejections - 35 USC § 112, Second Paragraph, New Rejection

Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 is rejected as being indefinite for the use of designation "rituximab" as the sole means of identifying the claimed antibody. The use of laboratory designation only to identify a particular antibody renders the claim indefinite because different laboratories may use the same laboratory designations to define completely distinct antibodies. Amendment of the claim to include physical and/or functional characteristics of which unambiguously define "rituximab", for example, by adding "which is a humanized anti-CD20 monoclonal antibody", is required.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
June 20, 2006

SUSAN UNGAR, PH.D
PRIMARY EXAMINER